Step 13: DTx Product Evaluation Types

Digital therapeutics undergo multiple evaluations throughout the product life cycle. These clinical and economic studies are used in the evaluation of product safety, effectiveness, real-world use, implementation, value assessment, and therapy optimization. In general:

- **Regulatory oversight:** Clinical pre-market evaluations are generally required to secure regulatory clearance and/or CE marking.
- **Coverage and reimbursement:** Clinical trials and economic evaluations are generally required for initial payor assessments.
- **Clinical practice:** Clinical trials and real-world data (RWD) are generally used to determine direct patient care and clinician decision making.
- **Clinical guidelines:** Clinical trials and real-world evidence (RWE) are generally used for DTx product incorporation into clinical guidelines.

The following overview provides the types of evaluations that a DTx product have undergone. Healthcare decision makers (HCDM) should conduct a thorough review of study design, outcomes, and quality of evidence.

<table>
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<tr>
<th>Number completed</th>
<th>Number in progress</th>
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**Observational Studies**

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<tr>
<td></td>
<td>Descriptive: Case report, case series, cross-sectional (descriptive or prevalence)</td>
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<tr>
<td></td>
<td>Analytical: Cross-sectional survey, case-control, cohort (prospective or historical)</td>
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<td></td>
<td>Implementation pilot: Assess site-specific implementation capacity and value</td>
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<td>Localization pilot: Assess cultural adaptation, language translation, linguistic accuracy/validation, etc.</td>
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<td>Other:</td>
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**Experimental/Interventional Clinical Trials**

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<tbody>
<tr>
<td></td>
<td>Randomized Controlled Trial (RCT)</td>
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<td></td>
<td>Other controlled trials: Non-randomized controlled trial, self-controlled study, crossover study</td>
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<tr>
<td></td>
<td>Non-controlled studies: Prospective single arm trial, open label trial, head-to-head comparative trial</td>
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<td>Other:</td>
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**Real-World Outcomes**

**RWD generation:**

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<tr>
<td></td>
<td>Product performance and technical outputs</td>
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<tr>
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<td>End user and clinician engagement and satisfaction measures</td>
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<td></td>
<td>Other:</td>
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**RWE generation:**

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<tr>
<td></td>
<td>Pragmatic clinical trial using an RCT-type design, with real-world elements</td>
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<tr>
<td></td>
<td>RWE as a retrospective or prospective observational study</td>
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<td></td>
<td>Other:</td>
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</tbody>
</table>
### Number completed | Number in progress
---|---

**Product Analyses**

- **Retrospective analyses**: chart reviews, medical/pharmacy claims, electronic medical records, other novel data sources
- **Expert reviews**: clinical practice guidelines, clinical pathways, Health Technology Assessment (HTA) agency evaluations, published systematic reviews
- **Coverage decision assessments and formulary reviews**: external organization product evaluations, product indication reviews
- **Patient perspectives**: insight into the practical use of therapies
- **Other**:

**Economic Evaluation**

- **Budget impact analysis**
- **Cost-benefit analysis**
- **Cost-effectiveness analysis**
- **Cost-utility analysis**
- **Cost-minimization analysis**
- **Other**:

**Systematic Review**

- **Meta analysis**
- **Other**:

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Step 14: Assessing Clinical Evidence Types

Digital therapeutics undergo clinical evaluations to assess product safety and clinical efficacy. Outcomes may also be used to determine therapy effectiveness, how the therapy should be used in target settings, length of therapy duration, the types of patients who may benefit, and appropriate use in clinical practice. Strong outcomes in studies often correlate to higher performing, lower risk products; reliable clinical outcomes and performance; and increased overall value of investment.

Check all that apply.

**Study Basics**

Study name: ________________________________________________________________

Publication name and citation: ________________________________________________

Trial registry number: _______________________________________________________

Was the study protocol modified after registering in clinicaltrials.gov or a similar registry? □ Yes □ No

If yes, describe how: _______________________________________________________

Study status:

☐ Study is currently underway
☐ Study is completed, but not published
☐ Study is completed and published
☐ Study forms the basis for regulatory clearance, CE marking, and/or product marketing claims
☐ Other: _________________________________________________________________

Study partners (i.e., university, CRO): _______________________________________

Sponsor or funding source(s): ______________________________________________

Has this study been peer-reviewed? □ Yes □ No □ Undergoing peer-review process

**Study Design**

Clinical study design used:

☐ Non-randomized controlled trial
☐ Prospective, single arm trial
☐ Cohort study
☐ Case-control study
☐ Case study
☐ RCT
☐ Pragmatic clinical trial
☐ RWE
☐ Other: _________________________________________________________________

Study start and completion dates: ___________________________________________

Study setting(s) and geographic location(s): ___________________________________

Trial design, randomization, and blinding procedures: _________________________
Study Population

Target population and subgroups: ____________________________________________

Inclusion criteria: ________________________________________________________

Exclusion criteria: ________________________________________________________

Baseline patient characteristics and demographics: ____________________________

Study population is representative of:

☐ General population

☐ Target population

☐ Other: ________________________________________________________________

To mitigate bias, datasets are balanced across:

☐ Gender

☐ Ethnicity

☐ Age

☐ Other: ________________________________________________________________

Clinical Outcomes

Key findings of the study: _________________________________________________

Primary endpoint: _______________________________________________________

Secondary endpoints: ____________________________________________________

Comparator used: _______________________________________________________

Treatment and intervention used, dosing regimen: ____________________________

Concomitant therapies, washout period: _____________________________________
Step 15: Assessing Quality of Clinical Evidence

Given the importance of clinical evidence in determining a DTx's clinical impact at the patient and population levels, HCDMs are encouraged to evaluate the quality of each study being submitted as part of the product's dossier.

Therefore, DTx manufacturers are asked to provide the following criteria based upon the tenets of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework per submitted clinical study.1

Checked all that apply.

This study accounts for the following considerations:

Risk of Bias
- Potential limitations in the design or conduct of the study identified
- Conflicts of interest among study contributors identified
- Other:

Imprecision
- Study outcomes are inside of the 95% confidence interval
- The "n" is appropriate (i.e., a sample size that is powered appropriately for intended outcomes)
- Study analysis accounts for patient populations who have enrolled in the product, in addition to those who have been included in the study but declined participation
- Analytic methods address potential skewed, missing, or censored data; approaches to study adjustments; or population heterogeneity and uncertainty
- Other:

Inconsistency
- Multiple studies suggest similar clinical outcomes and have consistent confidence intervals
- Similarity between statistical and clinical significance relative to sample size
- Large magnitude of effect
- Other:

Indirectness
- Patients studied are similar to those for whom the clinical recommendation applies
- Interventions studied reflect actual practice
- Outcome studied is a surrogate for the appropriate outcome
- Other:

Publication Bias
- Potential holes in evidence are accounted for
- Outcomes are generated from experimental/interventional data
- Published studies underwent a peer-review process
- Other:

1 https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/
Step 16: Types of Real-World Data (RWD) Generated by DTx Products

Through their ongoing use in patient care settings, DTx products generate a wide variety of RWD and outcomes that:

» Are made available to patients, caregivers, clinicians, and payors in line with patient privacy protections
» Form the foundation of decisions by clinicians and clinical teams
» Directly factor into RWE and economic analyses

With increasing frequency, DTx-generated outcomes and measures are replacing or supplementing outcomes generated through non-digital methods.

Check all that apply.

Digital therapeutics generate one or more types of RWD, outcomes, and insights depending on the product's purpose and functionality. Although this list is not comprehensive and will evolve, examples of RWD this product is able to produce include:

Clinical Measures

☐ Clinical outcomes (i.e., respiratory control, mobility, mental health status, FIM scores)
☐ State of medical condition (i.e., disease state severity, comorbidities)
☐ Digital endpoints (i.e., measures not previously available or assessed)
☐ Digital biomarkers (i.e., walking gait, joint mobility)
☐ Standardized patient assessments (i.e., GAD-7, PHQ-9, PSS)
☐ Patient-reported outcomes (PROs) (i.e., validated outcome measures, disease state triggers, pain perception)
☐ Physiologic data via associated sensors and hardware (i.e., pulse, breathing rates, blood pressure)
☐ Insight on related therapies (i.e., medication use and dosages, adherence patterns)
☐ Degree of disease state severity and change (i.e., condition improvement, deterioration)
☐ Other: ________________________________

Product Functionality

☐ Product performance (i.e., product up/down time, functionality, internet connectivity)
☐ Analytics (i.e., system or product performance, efficiency)
☐ Quality measures (i.e., HEDIS, CAHPS measures)
☐ End user satisfaction measures (i.e., product acceptability, perceived helpfulness)
☐ Interoperability (i.e., EHR integration, performance related to connected or affiliated devices)
☐ Other: ________________________________

Patient and Clinician Utilization

☐ User demographic data (i.e., age, gender, ethnicity)
☐ User geolocation (i.e., country, state, region)
☐ Utilization flow (i.e., gestural data, behavioral flow, performance data, utilization metrics)
☐ Patient engagement (i.e., time, frequency, duration of product utilization)
☐ Patient onboarding (i.e., consent documentation, patient/caregiver training, patient preferences)
☐ Patient utilization (i.e., registration, downloads, screen time usage, long-term retention)
☐ Patient adherence (i.e., completed vs. recommended modules, exercises, or lessons)
- Patient open-ended comments (i.e., patient preferences, satisfaction, surveys)
- Clinician inputs (i.e., prescribing parameters, authorization and discontinuation orders)
- Clinician engagement (i.e., registrations, initial and ongoing activity)
- Clinician implementation (i.e., utilization, frequency of use)
- Patient-clinician communications (i.e., scheduling, messaging)
- Patient, caregiver, clinician support service utilization (i.e., service type, frequency)
- Other:
Step 17: Utilizing DTx-Generated RWD

Compared to traditional medications, DTx products uniquely generate RWD, which includes a wide variety of data sets related to patient outcomes and product performance. RWD is generated on an ongoing basis by DTx products as a result of patient product use and is made available to patients and appropriate stakeholders in alignment with privacy and patient consent requirements.

**Check all that apply.**

**How are DTx-generated RWD outcomes used in practice?**

- Provide patients and caregivers with real-time insights on therapy progress and outcomes
- Generation of clinically actionable data to inform clinical decision making and optimize patient therapies
- Safety surveillance and adverse event identification
- Analysis of individual, subpopulation, and population trends and outcomes
- Payor-level de-identified data analysis for research purposes
- Short-term product functionality improvement and bug identification
- Long-term product improvement and iteration
- Other: ____________________________

**What additional data sources may be merged with DTx-generated RWD?**

- Outputs from sensors, wearables, and other product plug-ins
- Validated patient assessment tools
- Electronic health record (EHR) and healthcare claims data
- Disease registry lists and outcomes
- Patient-generated insights
- Other: ____________________________

**Who is responsible for analyzing and delivering RWD outcomes?**

- DTx manufacturer
- Health system
- Clinician
- HCDM/payor
- Other: ____________________________

**What level of the DTx-generated data source chain may reviewers and clinicians see?**

- Raw data
- Processed data
- Data trends
- Other: ____________________________

**Commentary:** RWD serves a vital role in the patient care continuum. Given the different purposes that RWD and RWE serve, when RWD is available, it may not be necessary to conduct a formal RWE study for direct patient care purposes. DTx-generated RWD is reliable and provides immediate and ongoing patient-specific insights.
Step 18: Development and Impact of Real-World Evidence (RWE)

Compared to RWD that is generated by DTx products on an ongoing basis and used by patients and clinicians in real time, RWE is developed through a formal clinical trial design process. RWE involves the formal analysis of RWD and other data sources to answer a specific clinical question related to the DTx product or related therapies, often conducted in the form of a prospective or retrospective observational study.

Check all that apply.

Conducting an RWE Study

What situations are most appropriate to develop RWE for this product?

- Inform a population-level decision
- Assess long-term DTx product clinical impacts
- Demonstrate that treatment effects are reproduced in broader populations or new clinical use settings
- Provide insights beyond those gathered in RCTs and RWD
- Assess DTx product use in a health system workflow
- Conduct a formal economic impact analysis
- Demonstrate impact on costs by using RWD in clinical practice
- Undertake a contractual requirements analysis (i.e., outcomes or value-based contracting)
- Other: ________________

When may it not be necessary to conduct an RWE study?

- RCT and other studies have already demonstrated sufficient safety, efficacy, effectiveness, and economic outcomes for formulary placement and coverage decisions
- DTx-generated RWD data and analysis provide sufficient outcomes and metrics for clinicians and HCDMs
- System data analyses provide sufficient insights for clinical and economic assessments
- Other: ________________

Benefit of RWE Studies

Which target groups are most likely to benefit from an RWE study for this product?

- Regulatory (i.e., post-market surveillance, product claims expansion)
- Clinicians (i.e., point-of-care decisions, determining how DTx use impacts other therapies and clinical outcomes, assessing short- and long-term health impacts)
- Patients (i.e., decisions related to healthcare options)
- HCDMs and payors (i.e., economic reviews, formulary review assessment, product use case evaluations, general research, risk reduction dashboards, quality improvement projects, population impact evaluations, background for future contractual considerations)
- Clinical guideline developers (i.e., clinical practice guideline decisions)
- Policy makers (i.e., product impact on populations, disease state improvements)
- Industry stakeholders (i.e., life sciences organizations)
- Other: ________________
Evaluating an RWE Study

If the DTx manufacturer submits an RWE study as part of this Guide, the following criteria may be used to assess the trial.

Study name: ________________________________

Study citation: ______________________________

Who was responsible for conducting this RWE study?

- DTx manufacturer
- Health system or clinical team
- Employer
- Payor
- Academic institution
- Third-party entity
- Other: ________________________________

What inputs were included in this RWE study?

- DTx-generated RWD outcomes
- Outputs from other devices, sensors, wearables, and plug-ins
- Health system sources (i.e., data from claims databases, EHRs, disease state registries)
- Other: ________________________________

What considerations were incorporated in the RWE study design?

- Demonstrates that it is fit-for-purpose and of appropriate rigor
- Involves key stakeholders in designing and/or informing RWE studies
- Has pre-specified objectives, including specific hypotheses and target populations
- Ensures that data are collected and analyzed per pre-established protocols
- Provides opportunities to replicate study and outcomes
- Represents the real-world patient population
- Evaluates statistical significance and clinical meaningfulness in a representative sample of patients with the condition being treated
- Other: ________________________________

RWE study outcomes are:

- Meaningful, providing relevant and context-informed evidence sufficient for interpretation, drawing conclusions, and making decisions
- Valid, meeting scientific and technical quality standards to allow causal interpretations
- Expedited, with incremental evidence synchronized with the decision making process
- Transparent, auditable, and reproducible
- Impactful, providing outcomes related to disease-specific healthcare resource utilization, evaluation of total healthcare resource utilization, etc.
- Other: ________________________________
Where is/will the RWE study results be published?
- Publicly, in a peer-reviewed publication
- Publicly, available in a white paper
- Internal analysis (i.e., informal report, formal report)
- Other: ____________________________

Who has/will have access to RWE study results?
- HCDM and/or payor
- HTA or formulary review committee
- Point-of-care clinician
- Patient and/or caregiver
- Publicly available
- Other: ____________________________
Digital Therapeutics Alliance

Founded in 2017, the Digital Therapeutics Alliance (DTA) is a non-profit trade association of industry leaders and stakeholders engaged in the evidence-driven advancement of digital therapeutics. As the leading international organization on digital therapeutic thought leadership and education, DTA provides patients, clinicians, payors, and policy makers with the necessary tools to evaluate and utilize DTx products.

DTA’s members—including organizations dedicated to manufacturing, evaluating, supporting, and utilizing DTx products—work to transform global healthcare by advancing high-quality, clinically validated digital therapeutics to improve clinical and health economic outcomes.